Factors influencing the response to chemotherapy in human cystic echinococcosis

T. Todorov,[1] G. Mechkov,[2] K. Vutova,[3] P. Georgiev,[4] I. Lazarova,[5] Z. Tonchev,[6] & G. Nedelkov[7]

As the effectiveness of mebendazole and albendazole in patients with echinococcosis has been found to vary, we investigated some of the factors likely to be responsible. A total of 79 patients who were treated with mebendazole (44 patients) or albendazole (35 patients) were included in the study. Evaluation of the treatment results was based on the changes in cyst morphology, as evidenced by the results of X-ray radiography, sonography, and computed tomography, and on analysis of the findings in relation to parasitic and drug factors. The response of cysts according to their site did not vary much, with the exception of the poor response of bone cysts. A more important factor seems to be cyst size, since the treatment was more efficacious against smaller and younger cysts. The presence of daughter cysts should be regarded as an unfavourable factor for treatment response. Cyst multiplicity did not present insurmountable difficulties, provided the cysts were small and a prolonged course of therapy was undergone. The choice of drug used for the therapy was important, with the results supporting the advantage of albendazole. In planning the chemotherapy of hydatid disease, factors such as cyst condition and drug used should therefore be taken into consideration.

Human cystic echinococcosis was, until recently, a disease for which the only treatment was surgical intervention. Over the last 10 years, however, two benzimidazole compounds, mebendazole and albendazole, have been tested clinically for use in the chemotherapy of hydatid disease. Some workers have reported encouraging results following therapy with both these benzimidazoles, varying from stabilization to complete disappearance of hydatid lesions (*1–10*). Other reports, however, have described less favourable outcomes and even treatment failures (*11–13*). Explanations for these differences in outcomes have been discussed by several investigators (*14–16*).

In a previous article on the chemotherapy of liver echinococcosis, we reported variable cyst responses and postulated that factors such as the condition of the cyst, the drug used, and the duration of the treatment could be connected with differences in the observed treatment results (*15*). However, these factors, which appear to be essential for the individual patients treated, and which appear not to be identical for single, multiple, and multiorgan hydatid cysts, have not yet been thoroughly investigated. It is therefore of interest to evaluate these factors in detail. In the present article we describe the results of treating patients with hydatid disease using two benzimidazolecarbamates — mebendazole and albendazole — and of our analysis of the role that some factors might play in influencing their effectiveness.

Patients and methods

A total of 79 patients with cystic echinococcosis were included in the study. Of these patients, 47 had cysts in a single organ, while for the remaining 32 patients cysts were located in two or three organs (Table 1). The number of cysts varied considerably: 28 (35%) patients being affected with 1–2 cysts; 10 (13%) with 3–4 cysts; 17 (21%) with 5–7 cysts; 5 (6%) with 8–10 cysts; and 11 (14%) with over 10 cysts. For the eight patients (10%) with bone echinococcosis the number of cysts could not be determined. The estimation of the number of cysts in each patient was performed separately by three of us (I.L.,

[1] Senior Lecturer in Parasitology, Institute of Pharmacology, Medical Academy, P.O. Box 54, 1431 Sofia, Bulgaria. Requests for reprints should be sent to this author.

[2] Professor and Head, Department of Gastroenterology and Phytotherapy, and President, Military Medical Academy, Sofia, Bulgaria.

[3] Assistant, Department of Parasitology and Tropical Medicine, Institute of Infectious and Parasitic Diseases, Medical Academy, Sofia, Bulgaria.

[4] Chief, Gastroenterology Clinic, Military Medical Academy, Sofia, Bulgaria.

[5] Assistant, Department of Radiology, Medical Academy, Sofia, Bulgaria.

[6] Associate Professor, Radiology Clinic, Military Medical Academy, Sofia, Bulgaria.

[7] Associate Professor, Department of Radiology, Medical Academy, Sofia, Bulgaria.

Reprint No. **5286**

Table 1: **The sites of the hydatid cysts and the treatment received by the patients in the study**

Site	No. of patients treated with: Mebendazole	Albendazole	Total
Liver	17	10	27
Lungs	6	3	9
Spleen	1	—	1
Abdomen	1	—	1
Brain	—	1	1
Spine	—	1	1
Pelvic and femoral bones	3	3	6
Liver and spine	—	2	2
Liver and lungs	5	2	7
Liver and brain	1	1	2
Liver and abdomen	3	5	8
Liver and spleen	1	—	1
Lungs and spleen	—	1	1
Abdomen and spleen	1	—	1
Liver, lungs, and spleen	2	1	3
Liver, spleen, and abdomen	3	4	7
Total	44	35	79

Z.T., and G.N.), based on the results of radiography, ultrasonography, and computed tomography. The arithmetic mean of the three estimations was taken as the number of cysts for an individual patient. The average error was in the range ± 1–3. Cyst size was measured in cm (diameter).

A total of 44 cases were treated with mebendazole (22 females and 22 males; mean age, 42 years; range, 6–70 years) and 35 cases with albendazole (16 females and 19 males; mean age, 40 years; range, 10–66 years). Mebendazole[a] was given at a dosage of 30–70 $mg.kg^{-1}.day^{-1}$ for 6–24 months (mean, 9.4 months; mean total dose per patient, 1250 g; mean follow-up period, 31 months). The dosage of albendazole[b] was 10 $mg.kg^{-1}.day^{-1}$ for four courses of 30 days, with an interval of 15 days between courses (mean duration, 5.5 months including intervals; mean total dose per patient, 82 g; mean follow-up period, 33 months). Nine patients initially treated with mebendazole and three with albendazole, for whom the outcome was only partly successful (4 cases) or unsuccessful (8 cases), were retreated with mebendazole (3 cases) and albendazole (9 cases).

The pretreatment diagnosis of hydatid disease and the assessment of changes in cyst morphology were performed at regular intervals in accordance with WHO protocols using radiography, ultrasonography and computed tomography.[c, d] Hydatid disease was confirmed using at least four immunodiagnostic tests.[e]

The degree of cyst response was based on the changes in cyst appearance as observed by X-rays,

[a] Janssen Research Foundation, Beerse, Belgium, and Gedion Richter, Budapest, Hungary.

[b] SmithKline Beecham, Mundells, Welwyn Garden City, England.

[c] *Informal WHO meeting on the treatment of human echinococcosis, Geneva, 19 June–1 July 1981: treatment of human echinococcosis.* Unpublished WHO document PDP/82.1.

[d] *Treatment of human echinococcosis: report of an informal meeting.* Unpublished WHO document PDP/84.6.

[e] **Todorov, T.** [*Humoral immune response in echinococcosis*]. D.Sc. Dissertation. Medical Academy, Sofia, 1980, pp. 61–74 and 80–262 (in Bulgarian).

ultrasonography, and computed tomography, as described previously (*4*).

Results

Diagnosis

The following serological tests — indirect haemagglutination (IHAT), latex agglutination (LAT), indirect immunofluorescent (IIFT) and enzyme-linked immunosorbent assay (ELISA) — were used to confirm or reject the diagnosis of suspected hydatid disease based on the results of radiography, sonography, and computed tomography. Patients who were negative were retested after 6 months, and those with negative serology were excluded from the study. Hydatid disease was considered to have been confirmed when at least two immunodiagnostic tests were positive (the minimal diagnostic titres were as follows: IHAT, 1: 200; LAT, 1: 5; IIFT, 1: 20; and ELISA, 31%.)

Usually, the immune responses were not uniform, but differed considerably, depending on the tests used and on the condition of the cysts. In general, the IHAT titres (the most sensitive test) were higher than those of the other tests, ranging from 1: 800 to 1: 204 800, while those for LAT lay in the range 1: 5 to 1: 2560, those for IIFT, 1: 20 to 1: 1280, and those for the ELISA, 36%–148%. The serological tests were less sensitive for patients with pulmonary and bone echinococcosis, where low titres predominated. The tests for the group with liver, abdominal, and multiorgan cysts were more sensitive and higher titres were characteristic.

Evaluation of responses

In the evaluation of the treatment responses, each hydatid cyst was considered as a separate parasitic unit, except in cases with bone echinococcosis. This approach was chosen since not all cysts with the same localization responded equally to chemotherapy, and it was essential to evaluate the changes in each cyst. The chemotherapy results were analysed in terms of parasitic (such as cyst localization, size, age, number, and structure) and drug factors.

Cyst factors

Cyst localization. Response to therapy, according to cyst site, after treatment with both mebendazole and albendazole is shown in Table 2. There was no significant difference between the proportions of positive responses for cysts in the liver, lungs, and abdomen. The cysts in the spleen were less sensitive and those in the brain, more sensitive, but compared with the other cyst localizations the differences in response were statistically not significant ($P > 0.1$) (Fig. 1 and 2). The weakest response occurred for patients with bone echinococcosis, only two of whom with vertebra cysts responded positively and one of whom responded partially, while six exhibited no response (Fig. 3).

Cyst size. The response of the hydatid cysts to treatment according to their size is shown in Table 3. The highest proportion of positive responses was observed in cysts of diameter 1–3 cm. The proportion of positive responses for cysts of diameter 8–10 cm was 8.3%, which was statistically significantly lower than that for the other three groups of cysts of smaller diameter ($P < 0.001$). The smaller cysts disappeared from the parenchyma, while the larger ones remained unchanged in size (Fig. 4 and 5).

Cyst number. The responses of cysts according to their number is shown in Table 4. The highest proportion of positive responses (71.1%) occurred in patients with over 10 cysts, was lower in those with 3–5 and 6–10 cysts, and lowest (34.9%) in patients with 1–2 cysts; the differences were statistically significant ($P < 0.001$).

Cyst age. Cyst age was determined from the time that had elapsed since previous surgery in patients with recurrences and by the length of the case history. The proportions of positive responses for patients with cysts of age up to 5 years and 6–10 years were 59.4% and 48.5%, respectively (Table 5). These proportions were significantly higher than those for patients who had had cysts for more than 10 years ($P < 0.01$ and $P < 0.05$) (Fig. 4 and 6).

Cyst structure. For 10 patients with old and large single cysts (8–10 cm in diameter), daughter cysts were found inside the mother cyst. In eight of these patients the daughter cysts did not respond to treatment. The cysts of the remaining two patients responded partially, the walls becoming thicker and calcification spots developing, without any alterations in the daughter cysts (Fig. 7).

Drug factors

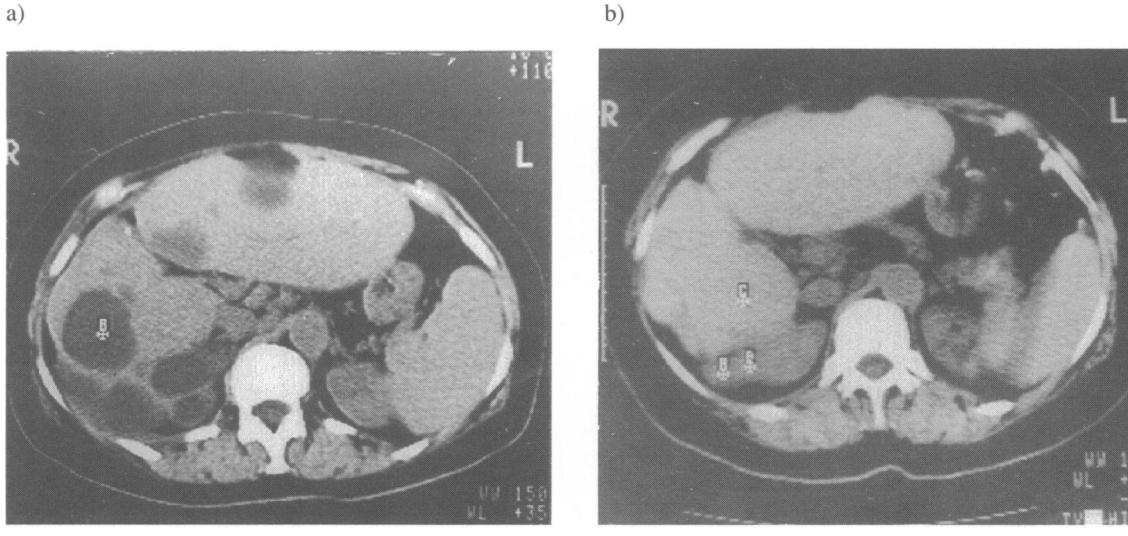
Drugs used. Cyst response to both mebendazole and albendazole, according also to organ localization, is shown in Table 6. The proportion of all cysts treated with albendazole that responded positively was 65.4%, which was statistically significantly higher ($P < 0.001$) than those treated with mebendazole

Table 2: **Response of the hydatid cysts to treatment with mebendazole and albendazole, according to the cyst site**

Site	No. of cysts treated	No. with positive response	No. with partial response	No. with no response
Liver	170	90 (52.9) [a]	12 (7.1)	68 (40.0)
Lungs	130	73 (56.2)	6 (4.6)	51 (39.2); $P > 0.10$ [b]
Brain	10	8 (80.0)	— —	2 (20.0); $P > 0.10$
Spleen	22	8 (36.4)	— —	14 (63.6); $P > 0.10$
Abdomen	79	43 (54.4)	6 (7.6)	30 (38.0); $P > 0.10$

[a] Figures in parentheses are percentages.
[b] P values are with respect to positive responses.

Fig. 1. **Computed tomograms of liver cysts:** a) Multiple liver cysts, 3–5 cm in diameter, before treatment; b) disappearance of the cysts 6 months after completing 6 months' therapy with albendazole.



(44.1%). This difference resulted from the better response of the liver and lung cysts in patients treated with albendazole. Altogether, 26.2% of the cysts treated with albendazole and 52.3% of those treated with mebendazole did not respond, and this difference was also statistically significant ($P < 0.001$). The difference between the proportions of cysts that responded partially was not statistically significant ($P > 0.10$).

Of the patients who received mebendazole, 10 (22.7%) were treated successfully, 9 (20.5%) partially, while for 25 (56.8%) the treatment failed (Table 7). In the albendazole group, the treatment was successful for 15 patients (42.8%), partially successful for 11 (31.4%), and failed for 9 (25.7%). The differences in efficacy between both drugs in terms of the therapeutic success or partial success were statistically not significant ($P > 0.10$). The difference was, however, significant in terms of therapeutic failure ($P < 0.05$).

Drug dosage and treatment duration. The mean total dose of mebendazole per patient was 1250 g; the mean treatment duration was 9.4 months. Successful treatment was observed with a mean total dose of 1700 g, partially successful, with a mean dose of 1130 g, while treatment failures received a mean dose of 910 g. The mean length of treatment for the three groups of efficacity was 14.4, 9, and 7.6 months, respectively. With albendazole the mean total dose per patient was 82 g and the mean treatment duration, 5.5 months, including the intervals between doses. For patients whose therapy was successful, partially successful, or which failed, the dif-

Fig. 2. **Computed tomograms of abdominal cysts:** a) Several hydatid cysts in the abdominal cavity before treatment (water-like density, 7–11 HU); b) disappearance of some cysts and reduction in size of others, with increased density (52–60 HU) 12 months after completing therapy with albendazole: HU = Hounsfield units.

a) b)

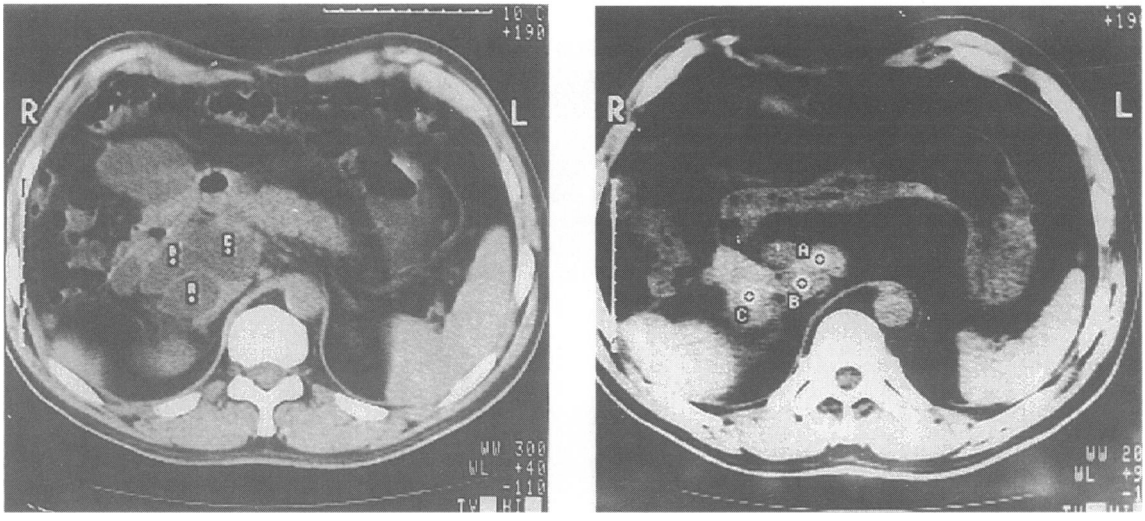
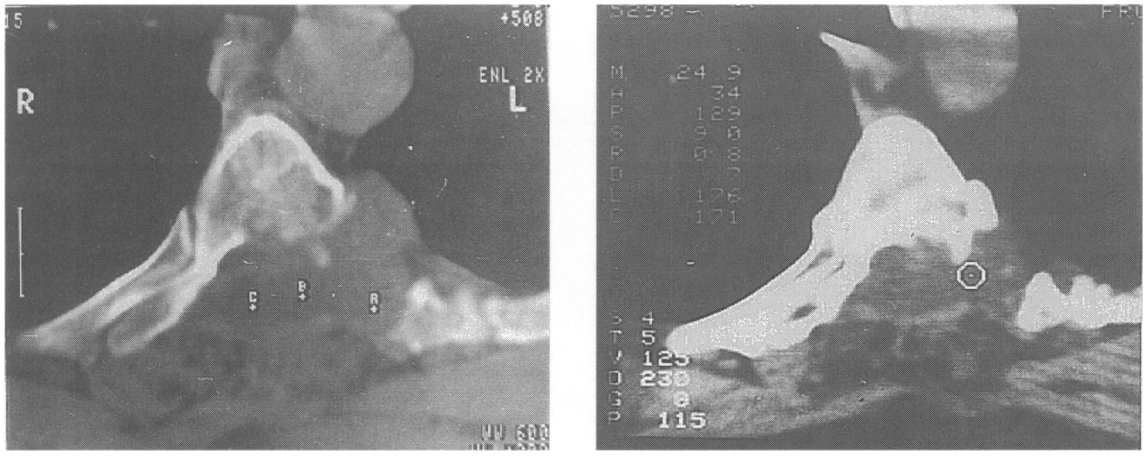


Fig. 3. **Computed tomograms of the Th4 vertebra of a patient with paraparesis of the lower extremities:** a) Partial destruction of the Th4 vertebra with two small cysts present, before treatment; b) reduction in cyst size 10 months after starting therapy with albendazole (after spinal decompression the patient became mobile).

a) b)



ferences in the mean total dose of albendazole were not statistically significant (doses: 80 g, 83 g and 85 g, respectively), the treatment duration remaining unchanged.

Of the 12 patients who underwent repeat therapy, four were successful, four, partially successful, while there was no change in the remaining four (Table 8).

Drug plasma concentration. In some patients there were definite correlations between the plasma levels of the drugs and the therapeutic results. High average

Table 3: **Response of the hydatid cysts to treatment with mebendazole and albendazole, according to cyst diameter**

Cyst diameter (cm)	No. of cysts treated	No. with positive response	No. with partial response	No. with no response
1–3	187	134 (71.7)[a]	11 (5.9)	42 (22.4)
4–5	118	61 (51.7)	7 (5.9)	50 (42.4); P <0.01 [b]
6–7	70	24 (34.3)	5 (7.1)	41 (58.6); P <0.001
8–10	36	3 (8.3)	1 (2.8)	32 (88.9); P <0.001

[a] Figures in parentheses are percentages.
[b] P values are with respect to positive responses.

Fig. 4. **Computed tomograms of liver cysts:** a) Several small and recent liver hydatid cysts (diameter, 2–4 cm) before treatment; b) disappearance of the cysts after 24 months' therapy with mebendazole.

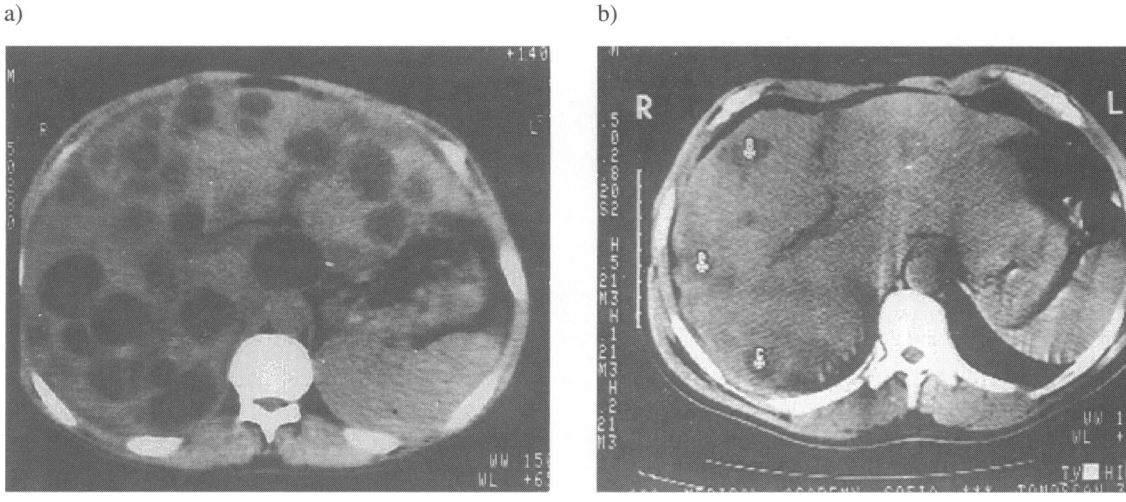


Fig. 5. **Radiological scans of pulmonary cysts:** a) Several small cysts in both lungs before treatment; b) disappearance of all cysts except two, which exhibited morphological deformation and structural changes 18 months after starting therapy with albendazole.

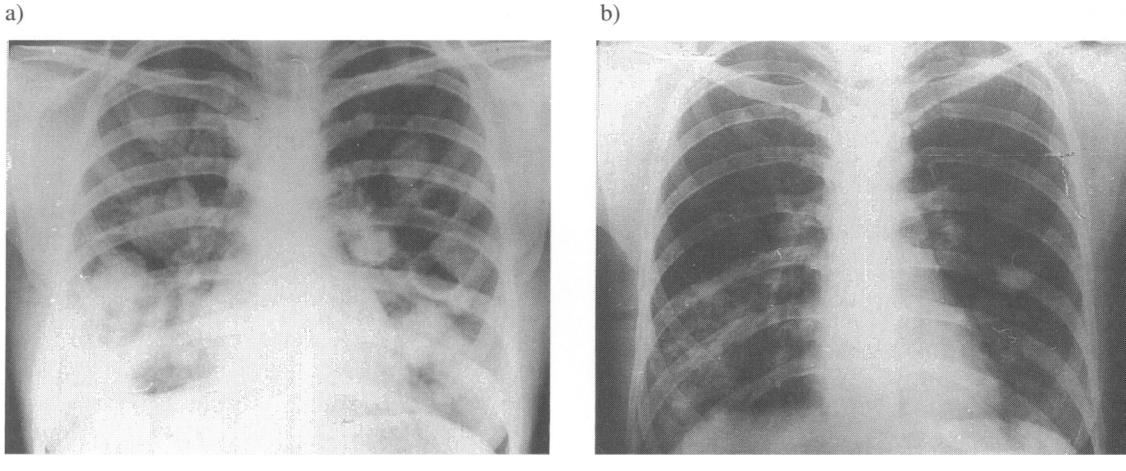


Table 4: **Response of the hydatid cysts to treatment with mebendazole and albendazole, according to the number of cysts in affected organs**

No. of cysts in affected organs	No. of cysts treated	No. with positive response	No. with partial response	No. with no response
1–2	43	15 (34.9) [a]	3 (7.0)	25 (58.9); $P < 0.001$ [b]
3–5	80	30 (37.5)	6 (7.5)	44 (55.0); $P < 0.001$
6–10	91	37 (40.6)	7 (7.7)	47 (51.6); $P < 0.01$
> 10	197	140 (71.1)	8 (4.1)	49 (24.9)

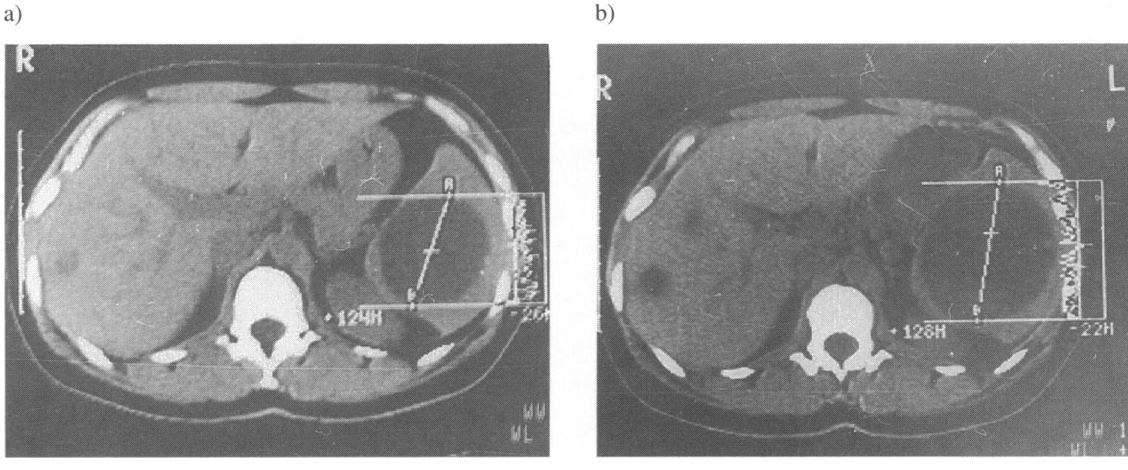
[a] Figures in parentheses are percentages.
[b] *P* values are with respect to positive responses.

Table 5: **Response of the hydatid cysts to treatment with mebendazole and albendazole, according to cyst age**

Cyst age (years)	No. of cysts treated	No. with positive response	No. with partial response	No. with no response
<5	256	152 (59.4)[a]	12 (4.7)	92 (35.9)
6–10	130	63 (48.5)	12 (9.2)	55 (42.3); $P > 0.10$ [b]
>10	25	7 (28.0	— —	18 (72.0); $P < 0.001$

[a] Figures in parentheses are percentages.
[b] *P* values are with respect to positive responses.

Fig. 6. **Computed tomograms of a spleen cyst:** a) Large, old spleen hydatid cyst (diameter, 63 mm) before treatment; b) enlargement of the same cyst (diameter, 80 mm) 12 months after completing 6 months' therapy with mebendazole.



plasma concentrations corresponded to successful treatment in some but not all the patients. Lower plasma levels were characterized for most of the patients by therapy failure, but there were exceptions.

Discussion

In many instances the diagnosis of hydatid disease presents difficulties because it has a broad clinical spectrum and has to be included in the differential diagnosis of abdominal, pulmonary, bone, and central nervous system pathology. Chest radiography, ultrasonography, and computed tomography are excellent and equally successful methods for this purpose, and we used them to define hydatid cysts, proving that they may affect more organs than would be expected, based only on the clinical picture.

Although the images of *Echinococcus granulosus* lesions obtained using these methods are almost

Fig. 7. **Computed tomograms of a liver cyst:** a) Large, old liver cyst with daughter cysts before treatment; b) the same cysts after 6 months' therapy with mebendazole (there were no changes in shape and structure).

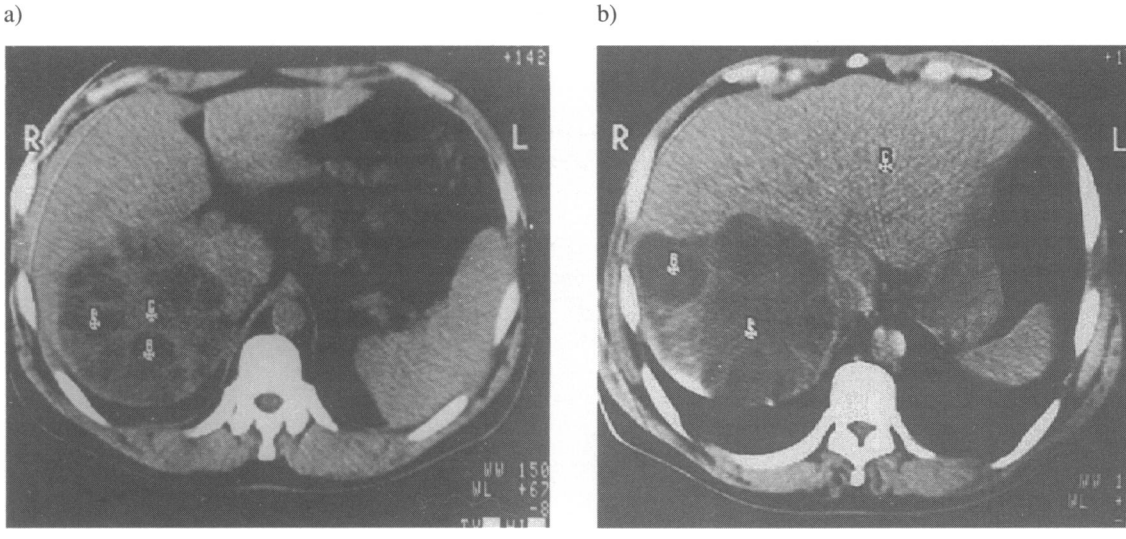


Table 6: **Comparison of the response of hydatid cysts to treatment with mebendazole and albendazole, according to cyst site**

	Mebendazole				Albendazole			
Site	No. of cysts examined	No. with positive response	No. with partial response	No. with no response	No. of cysts examined	No. with positive response	No. with partial response	No. with no response
Liver	99	43 (43.4)[a]	7 (7.1)	49 (49.5)	71	47 (66.2)	5 (7.0)	19 (26.8)
Lungs	79	32 (40.5)	— —	47 (59.5)	51	41 (80.4)	6 (11.8)	4 (7.8)
Brain	1	— —	— —	1 —	9	8 (88.9)	— —	1 (11.1)
Spleen	13	6 (46.7)	— —	7 (53.8)	9	2 (22.2)	— —	7 (77.8)
Abdomen	28	16 (57.1)	1 (3.6)	11 (39.3)	51	27 (52.2)	5 (9.8)	19 (37.2)
Total	220	97 (44.1) $P < 0.001$	8 (3.6) $P > 0.1$	115 (52.3) $P < 0.001$	191	125 (65.4)	16 (8.4)	50 (26.2)

[a] Figures in parentheses are percentages.

Table 7: **Comparative assessment of the chemotherapeutic efficacy of mebendazole and albendazole in the treated patients**

		Chemotherapeutic efficacy			
Drugs	No. of patients treated	No. successful	No. partially successful	No. of failures	
Mebendazole	44	10 (22.7)	9 (20.5)	25 (56.8)	
		$P > 0.1$	$P > 0.1$		$P < 0.05$
Albendazole	35	15 (42.8)	11 (31.4)	9 (25.7)	
Total	79	25 (31.6)	20 (25.3)	34 (43.1)	

Table 8: **Response of patients retreated with mebendazole and albendazole**

Patient	Site	Results after treatment with:	Results after retreatment with:
		Mebendazole	*Mebendazole*
1	Lungs	Partial success	Success
2	Liver and abdomen	Partial success	Partial success
3	Liver and lungs	Failure	Failure
			Albendazole
4	Lungs	Partial success	Partial success
5	Liver and brain	Failure	Partial success
6	Lungs	Failure	Success
7	Liver and lungs	Failure	Partial success
8	Liver, spleen, and abdomen	Failure	Partial success
9	Liver, spleen, and lungs	Failure	Success
		Albendazole	
10	Liver	Partial success	Success
11	Liver, spleen, and abdomen	Failure	Partial success
12	Bones	Failure	Failure

pathognomonic, difficulties may arise in making a differential diagnosis from simple cysts, polycystic liver disease, abscesses, subacute or chronic haematoma, haemangioma or other low-density abdominal or pulmonary mass, whether benign or malignant. In contrast, the results of serological tests are reliable but not infallible, since false-positive and false-negative reactions may occur. [f] We therefore made our diagnoses using a combination of radiography, ultrasonography and computed tomography, which permitted assessment of the number, size, localization and character of the cysts, and serology, establishing the parasitic etiology and assuring the specific diagnosis of our patients' lesions.

The results of the study confirmed the effectiveness of mebendazole and albendazole in human echinococcosis therapy that have been reported previously by other workers (*1–6*). The changes in cyst appearance following chemotherapy, as evidenced by the imaging methods used, suggest that both drugs affected directly the hydatid parasite, although with different degrees of effect. The results obtained showed that the morphological alterations in hydatid lesions occurred rapidly in some cysts but more slowly in others. Complete disappearance, reduction in size and cyst deformation, the most pronounced indications of a therapeutic effect, were observed for 54% of the cysts, while 40.1% remained unchanged and 5.8% were partly changed. In addition, analysis of the data showed that multiple cysts located in the same organ of a given patient underwent different changes. In an attempt to elucidate any anomalies in therapeutic responses, we hypothesized that certain factors might influence the efficacy of the drugs and that their identification should provide an explanation for the variation observed. We assessed these factors in individual patients over an extended follow-up period (mean: 31 months for mebendazole and 33 months for albendazole), aiming to detect any cyst recurrences and to determine more precisely the degree of response.

With the exception of bone cysts, the response to the treatment of the cysts in different organs did not vary significantly. It is evident from the P values in Table 2 that the differences between the susceptibility of cysts with different localizations occurred by chance and are not statistically significant. Clearly, the significance of the cyst site is very limited and the differences in response could depend on other factors.

A more important factor seems to be the cyst size. This is underlined by the indirect correlation between the positive responses to the therapy and cyst size and also by the statistically significant differences in therapeutic efficacy between cysts of diameter 1–3 cm and 4–5 cm ($P < 0.01$) and between those of diameter 1–3 cm, 6–7 cm ($P < 0.001$), and 8–10 cm ($P < 0.001$) (Table 3). These P values determine the differences in positive response, cor-

[f] See footnote *e*, p. 348.

respond to a greater than 95% level of probability, and indicate that cyst size is an active factor that influences cyst response.

The treatment response according to the number of cysts requires more detailed interpretation. The *P* values in Table 4, which correspond to a probability of greater than 95%, show that the differences between the proportions of positive responses in patients with more than 10 cysts and those in patients with fewer cysts are statistically significant. These findings are not consistent with previous observations that single cysts may be more sensitive to chemotherapy than multiple ones (*17*). Clearly, the role of one or more alternative factors, not taken into consideration in the present study, have influenced the above-mentioned differences in responses. This discrepancy could be explained by cyst size. In our study, the positive response by the group with more than 10 cysts in affected organs refers in 93.7% of instances to cysts of diameter up to 5 cm, which are more susceptible to chemotherapy. With this exception, the treatment of multiple cysts in some patients was prolonged or repeated in order to produce better results. The number of cysts should be considered as a chance factor since it may depend on uncontrollable circumstances.

Younger cysts, which were detected earlier or caused by secondary echinococcosis, were treated more successfully than older ones. The level of treatment failures for cysts associated with more than 10 years of disease history was significantly higher than that for younger cysts. The walls of the older cysts were thicker, as indicated by computed tomography and ultrasonography, suggesting that drug penetration into the cysts was poorer; in contrast, the susceptibility of the younger cysts is probably connected with the easier diffusion of the drugs across the thinner cyst membrane.

The role played by the drug used should be considered primarily in connection with its effect on hydatid cysts. The effect of albendazole was greater than that of mebendazole. The differences referred to as "positive" and "no" cyst responses were statistically significant, since the *P* values corresponded to a level of probability greater than 95%. The "insignificant" difference referred to partial responses, and could be explained by the insufficient number of cysts in this group.

The above conclusion that albendazole had a better therapeutic effect was expected to be supported by the final effectiveness in individual patients; however, this was not observed. The differences between the percentages of therapeutic successes among patients treated with both drugs were statistically insignificant; and this included also partial success. The better effectiveness of albendazole was confirmed only relative to patients who were treatment failures, the difference being statistically significant.

Analysis of the drug dose used showed that with mebendazole the treatment was successful if the mean total dose per patient was increased to 1700 g and that with lower doses partial success or failure should be expected. These results were also influenced by the duration of the treatment—the longer the treatment with mebendazole, the better the results. This was not observed with albendazole, which is an additional advantage of this drug.

Our study showed that in some cases prolonged treatment as well as retreatment was needed in order to improve the effectiveness of the therapy. However, successful results could not always be expected since the outcome depended on parasitic factors and on the drugs used.

In the analysis of the correlation between the concentration of the drug in plasma and the effectiveness of the therapy, it should be noted that the results differed considerably. Some data supported clearly a direct relationship between drug levels and effectiveness; however, no such correlation was found in other instances. High plasma levels of a drug did not always lead to treatment success. Probably the parasitic factors also played a distinct role on the chemotherapeutic effect of the drugs used.

Our investigations showed that both mebendazole and albendazole can be useful in treating patients with hydatid disease. However, in planning the chemotherapy of human cystic echinococcosis and predicting the outcome, factors such as the condition of the cysts, the drug used, and the duration of the treatment should be taken into consideration.

Acknowledgements

Professor J. Eckert, University of Zurich, is thanked for performing the indirect immunofluorescence test and enzyme-linked immunosorbent assays. We thank Janssen Research Foundation, Beerse, Belgium, and Gedeon Richter, Budapest, Hungary, for supplying mebendazole tablets, and SmithKline Beecham, Mundells, Welwyn Garden City, England, for supplying albendazole tablets. The financial support received from the WHO Parasitic Diseases Programme, is gratefully acknowledged.

Résumé

Influence de certains facteurs sur la réponse à la chimiothérapie dans l'hydatidose humaine

Le mébendazole et l'albendazole ont une efficacité variable chez les malades atteints d'hydatidose. Des résultats encourageants ont été rappor-

tés par certains auteurs, tandis que d'autres ont observé des réponses moins favorables et même des échecs thérapeutiques. Dans le présent article sont exposés les résultats du traitement de malades atteints d'hydatidose par le mébendazole et l'albendazole, deux benzimidazolecarbamates, dans le cadre d'une étude visant à déterminer en détail le rôle de certains facteurs dans la réponse thérapeutique.

L'étude a porté sur 79 malades porteurs de kystes en différents sites et en nombre variable. Quarante-quatre malades ont été traités en continu par le mébendazole à raison de 30–70 mg/kg par jour pendant 6 à 24 mois, et 35 malades ont été traités par l'albendazole à raison de 10 mg/kg par jour en quatre cures de 30 jours séparées par une fenêtre thérapeutique de 15 jours. Le diagnostic initial et l'examen des modifications de la morphologie des kystes ont été réalisés par radiographie, échographie et scanographie, et confirmés par plusieurs tests immunodiagnostiques. Les résultats de la chimiothérapie ont été analysés en fonction de plusieurs facteurs, les uns liés aux parasites et les autres aux médicaments.

La réponse des kystes en fonction de leur localisation variait peu, à l'exception d'une faible réponse dans le cas des kystes osseux. En général, la localisation du kystes n'avait pas d'influence significative sur l'efficacité thérapeutique des médicaments. La taille du kyste semblait un facteur plus important, les kystes les plus petits étant plus sensibles au traitement que les gros, avec une différence statistiquement significative. Les kystes jeunes étaient également plus sensibles au traitement que les kystes anciens, pour lesquels les échecs thérapeutiques étaient significativement plus nombreux. La meilleure réponse thérapeutique observée ches les kystes jeunes de petite taille est probablement due à une meilleure pénétration du médicament à travers la membrane qui est plus fine. Une plus forte proportion de réponses positives a été observée chez les malades ayant plus de dix kystes que chez ceux porteurs d'un kyste unique; cette observation est en contradiction avec les observations antérieures selon lesquelles les kystes uniques seraient plus sensibles à la chimiothérapie que les kystes multiples. Toutefois, dans 93,7% des cas observés ici, lorsque les kystes étaient plus nombreux, ils étaient de petite taille. La présence de kystes filles est à considérer comme un facteur défavorable pour la chimiothérapie, le médicament devant alors traverser une double membrane.

Le médicament utilisé pour la chimiothérapie de l'hydatidose est vraisemblablement le principal facteur capable d'influencer l'issue du traitement. Les effets des différents traitements sont statistiquement significatifs, autant pour les réponses positives que pour les échecs, et les résultats montrent que l'albendazole pourrait être plus efficace que le mébendazole. Dans certains cas, la réponse au traitement dépend de la dose et de la durée du traitement, notamment avec le mébendazole. Pour améliorer le résultat chez certains malades, il est recommandé d'envisager un traitement prolongé, des posologies élevées, et une répétition des cures.

Les résultats de cette étude montrent que le mébendazole comme l'albendazole sont utiles pour traiter les malades atteints d'hydatidose. Toutefois, pour établir un plan de traitement et en prévoir les résultats, il faut tenir compte de facteurs tels que l'état des kystes, le médicament employé et la durée du traitement.

References

1. **Morris, D.L. et al.** Albendazole in hydatid disease. *British medical journal*, **296**: 103–104 (1983).
2. **Kern, P. et al.** Traitement au mébendazole de l'échinococcose. *Bulletin de la Société de Pathologie exotique*, **78**: 712–717 (1985).
3. **De Rosa, F. & Tegi, A.** First experience in the treatment of human hydatid disease with mebendazole. *Drugs under experimental and clinical research*, **11**: 875–878 (1985).
4. **Todorov, T. et al.** Albendazole treatment of human cystic echinococcosis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**: 453–459 (1988).
5. **Horton, R.J.** Chemotherapy of echinococcus infection in man with albendazole. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **83**: 97–102 (1989).
6. **Davis, A. et al.** Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bulletin of the World Health Organization*, **67**: 503–508 (1989).
7. **Teggi, A. et al.** Treatment of *Echinococcus granulosus* hydatid disease with mebendazole. *Journal of chemotherapy*, **1**: 310–317 (1989).
8. **Todorov, T. et al.** Chemotherapy of liver and pulmonary hydatid disease with mebendazole. *Therapy of infectious diseases*, **5**: 5–19 (1990).
9. **De Rosa, F. & Teggi, A.** Treatment of *Echinococcus granulosus* hydatid disease with albendazole. *Annals of tropical medicine and parasitology*, **84**: 767–772 (1990).
10. **Todorov, T. et al.** Evaluation of response to chemotherapy of human cystic echinococcosis. *British journal of radiology*, **63**: 523–531 (1990).
11. **Braithwait, P.A.** Long-term, high-dose mebendazole for cystic hydatid disease of liver. *Australian and New Zealand journal of surgery*, **51**: 23–27 (1981).

12. **Bryceson, A.D.M. et al.** Experience with mebendazole in the treatment of inoperable hydatid disease in England. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **76**: 510–518 (1982).
13. **Rudwan, M.A. et al.** Abdominal hydatid disease: follow-up of mebendazole therapy by CT and ultrasonography. *International surgery*, **71**: 22–26 (1986).
14. **Eckert, J.** Prospects for treatment of the metacestode stage of echinococcus. In: *The biology of echinococcus and hydatid disease.* London, George Allen & Unwin, 1986, pp. 250–284.
15. **Todorov, T. et al.** Chemotherapy of liver cystic echinococcosis. In: *Leber und Parasiten: Verhandlungsberichtder Schweizerischen Gesellschaft für Tropenmedizin und Parasitologie, Jahrestagung, Zurich, 23–25 November 1989*, pp. 70–72.
16. **De Rosa, F. et al.** Influence of patient's age and cyst's age on the therapy of human hydatid disease with benzimidazole carbamates. *Turkish journal of medical and biological research*, **1**(2): 70–74 (1990).
17. **Kammerer, W.S. & Schantz, P.M.** Long-term follow-up of human hydatid disease (*Echinococcus granulosus*) treated with a high-dose mebendazole regimen. *American journal of tropical medicine and hygiene*, **33**: 132–137 (1984).